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ORIGINAL ARTICLE

Brevundimonas vesicularis bacteremia resistant to trimethoprim-sulfamethoxazole and ceftazidime in a tertiary hospital in southern Taiwan

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KEYWORDS
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Length of hospital stay

Background: Over the past 20 years, *Brevundimonas vesicularis* has rarely been reported as a pathogen causing human infection. The clinical manifestations of *B. vesicularis* bacteremia and its susceptibility to antibiotics has not been characterized.
Methods: A retrospective study was conducted between 2006 and 2009 in a tertiary-care hospital in southern Taiwan.
Results: A total of 22 cases of *B. vesicularis* bacteremia were identified during the study with 86% being community-acquired primary bloodstream infections. Of the 22 patients, 15 (68%) presented with fever, fewer comorbidities, shorter hospital stays, lower mean creatinine levels (1.10 mg/dL vs. 1.74 mg/dL), lower aspartate aminotransferase levels (29.1 IU/L vs. 79.0 IU/L), and lower alanine aminotransferase levels (16.4 IU/L vs. 67.0 IU/L) when compared to afebrile patients. Among the bacterial isolates, 90.9% were susceptible to cefpirome, imipenem and piperacillin/tazobactam while 86.4% were susceptible to gentamicin, amikacin and ciprofloxacin. However, 63.6% of the bacterial isolates were susceptible to ceftazidime, and only 59.1% were susceptible to trimethoprim-sulfamethoxazole (TMP-SMX). The 30-day mortality rate from all causes was 4.5%.
Conclusion: B. vesicularis is able to cause community-acquired and low-mortality primary bloodstream infections. The resistance of *B. vesicularis* to trimethoprim-sulfamethoxazole and ceftazidime limits the choice of available antibiotics for treatment.
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Introduction

Brevundimonas vesicularis (formerly known as *Pseudomonas vesicularis*), a non-fermenting Gram-negative bacillus,[1,2] has been infrequently reported as a pathogen causing hospital-acquired infection.[3–5] Most cases of *B. vesicularis* infection are community-acquired.[4,6–11] *B. vesicularis* can be isolated from the human endocervix, natural soil environments, bottled water, and hospital environments including shower hoses, dental unit reservoirs and hydrotherapy pools.[12–15] *B. vesicularis* can cause arthritis, endocarditis, meningitis, peritonitis, and primary bloodstream infection in immunocompromised as well as immunocompetent patients.[3–11] Whether *B. vesicularis* causes severe morbidity or mortality remains unclear.

In this report, 22 cases of *B. vesicularis* primary bacteremia were identified in a tertiary-care hospital in southern Taiwan between 2006 and 2009. Trends of increasing number of episodes, diversity, and prognosis of *B. vesicularis* primary bacteremia were observed.

Materials and methods

Study design

From January 2006 to December 2009, the database of the Clinical Microbiology Laboratory of Chi-Mei Medical Center was reviewed to identify bacterial cultures from blood specimens positive for *B. vesicularis* at the 1330-bed tertiary-care hospital, which serves two million people in southern Taiwan. This study was approved by the institutional review board of Chi-Mei hospital (IRB No. 10006-007). A patient was considered to have *B. vesicularis* bacteremia when the bacteria was isolated from one or more separate blood cultures processed by the BACTEC FX system (Becton Dickinson, Sparks, MD, USA) and the patient presented with compatible clinical symptoms. All patients with manifestations of systemic inflammatory response syndrome (SIRS) were routinely subject to aerobic and anaerobic blood cultures with 7-day incubations before being reported as negative for *B. vesicularis*. SIRS was defined as a patient meeting any two of the following criteria: body temperature less than 36°C or greater than 38°C, heart rate greater than 90 beats per minute, tachypnea with more than 20 breaths per minute, arterial partial pressure of carbon dioxide less than 32 mmHg, white blood cell count less than 4000 cells/mm^3 (4 x 10^9 cells/L) or greater than 12,000 cells/mm^3 (12 x 10^9 cells/L); or the presence of greater than 10% immature neutrophils (band forms).[16] Patients with positive *B. vesicularis* bacteremia were included in the study with the exception of patients with polymicrobial bacteremia. Identification of *B. vesicularis* was performed using the APE 20 NE system (bioMérieux, Marcy L'etoile, France) or Phoenix-100 ID/AST (Becton Dickinson) automated system. All of the *B. vesicularis* isolates were tested for minimal inhibitory concentrations (MICs) by the agar dilution method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[17] We used *Staphylococcus aureus* (ATCC®29213), *Enterococcus faecalis* (ATCC®29212), *Escherichia coli* (ATCC®25922) and *Pseudomonas aeruginosa* (ATCC®27853) as quality control strains. Medical records were reviewed for demographic data, clinical manifestations, co-morbidities, antibiotic regimen and clinical outcomes.

Definitions

Primary bacteremia was defined as infection not specific to an anatomical site. A nosocomial infection was defined as any episode occurring >48 hours after hospitalization or <14 days after previous discharge. A community-acquired infection was defined as any episode occurring <48 hours after hospitalization or >14 days after previous discharge. Fever was defined as body temperature >37.8°C. The primary outcome was defined as 30-day all-cause mortality and co-morbidities were obtained from medical records. Inappropriate antibiotic therapy was defined as treatment that did not include an antibiotic agent active against *B vesicularis*, as determined by the *in vitro* agar dilution method given during the 48 hours after the identification of *B. vesicularis*.

Statistical analysis

Mean ± standard deviation (SD) was calculated for each continuous variable and percentages were calculated for categorical variables. Categorical variables were evaluated using the Fisher's exact test and continuous variables were evaluated using the Mann–Whitney U test. A p value <0.05 was defined as statistically significant. All statistical analyses were performed using version 17 of the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago, IL, USA).

Results

A total of 22 patients with *B. vesicularis* bacteremia were recruited during the study period (Table 1). The ratio of males to females was 0.83. The age of the patients ranged from 3 to 94 years, with an average of 62.7 years; 13.6% (3/22) of patients were younger than 20 years, whereas 50% (11/22) were older than 70 years. Of the 15 patients with underlying chronic illnesses, 31.8% (7/22) had hypertension, 22.7% had prior histories of stroke, and 18.2% (4/22) had malignancies. In total, 13.6% (3/22) of *B. vesicularis* bacteremia cases were healthcare-associated. The all-cause mortality rate was 4.5% (1/22). The only death was a 93-year-old female patient who acquired the bacteremia after admission, presented with shock and then passed away on day 24 of hospitalization. She had been treated with ceftazidime and the isolate from her blood culture was susceptible to ceftazidime [minimal inhibitory concentration (MIC) = 4 mg/L]. Out of 22 patients, 15 presented with fever at admission and these patients had fewer co-morbidities when compared to afebrile patients (1 vs. 2.6, p = 0.009). Laboratory analysis showed that febrile patients had lower levels of creatinine (1.10 mg/dL vs. 1.74 mg/dL), aspartate aminotransferase (29.1 IU/L vs. 79.0 IU/L), and alanine aminotransferase (16.4 IU/L vs. 67.0 IU/L) than afebrile patients (Table 2).

The length of hospital stay averaged 13.3 days for the 19 hospitalized patients (Table 3). Patients who had 3 or more underlying diseases stayed longer than those who had 2 or

Table 1 Demographic characteristics and initial manifestations of 22 patients with *B. vesicularis* bacteremia

Case	Gender	Age	Initial manifestation	Co-morbidity	Acquired source
1	F	78	Fever	HTN	Community
2	F	78	Abdominal pain	HTN, LC, CKD	Community
3	M	3	Fever	Nil	Community
4	M	55	Fever	Alcoholism	Hospital
5	F	93	Shock	CHF CKD	Hospital
6	F	32	Fever	Nil	Community
7	F	84	Fever	HTN, old CVA	Community
8	F	19	Fever	Nil	Community
9	M	48	Altered consciousness	Old CVA, HTN, CHF	Community
10	F	94	Shock	Uterine prolapse	Community
11	F	82	Altered consciousness	HTN, old CVA, Malignancy	Community
12	M	51	Fever	Nil	Community
13	F	74	Fever	HTN, old CVA, Parkinsonism	Community
14	M	78	Fever	COPD, old CVA	Hospital
15	F	69	Fever	Malignancy	Community
16	M	68	Abdominal pain	Nil	Community
17	M	76	Fever	Malignancy, CKD	Community
18	M	81	Respiratory distress	HTN, DM, Parkinsonism	Community
19	M	58	Fever	Malignancy	Community
20	F	7	Fever	Nil	Community
21	F	63	Fever	Nil	Community
22	M	75	Fever	Parkinsonism	Community

CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVA = cerebral vascular accident; DM = diabetes mellitus; F = female; HTN = hypertension; LC = liver cirrhosis; M = male; Nil = no known underlying disease.

less (3.71 days vs. 14.7 days, $p = 0.015$). Patients who were initially afebrile had longer hospital stays than those who were febrile (17.6 days vs. 8.2 days, $p = 0.043$) (Table 2).

Table 2 Comparison of demographic characteristics, laboratory data, and length of hospital stay between pyretic and apyretic patients

	Pyretic	Apyretic	*p*
No. of patients (%)	15 (68.2)	7 (31.8)	
Age (y)	54.8	77.7	0.052
No. of co-morbidities	1	2.57	0.009*
LOS (d)	8.2	17.6	0.043*
Laboratory data			
WBC (cells/μL)	10600	9728	0.633
Hb (g/dL)	12.1	11.1	0.306
Platelets (10^3 cells/μL)	248	209	0.363
CRP (mg/L)	84.9	23.4	0.347
Na^+ (mEq/L)	132	126	0.224
K^+ (mEq/L)	4.01	4.47	0.329
BUN (mg/dL)	25.7	42.4	0.114
Cr (mg/dL)	1.10	1.74	0.025*
AST (IU/L)	29.1	79.0	0.038*
ALT (IU/L)	16.4	67.0	0.021*

*$p < 0.05$.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cr = creatinine; CRP = C-reactive protein; Hb = hemoglobin; LOS = length of hospital stay; WBC = white blood cell.

Antimicrobial susceptibility tests revealed that 90.9% of *B. vesicularis* isolates were susceptible to cefpirome, imipenem and piperacillin/tazobactam, 86.4% were susceptible to gentamicin, amikacin and ciprofloxacin, 63.6% were susceptible to ceftazidime and only 59.1% were susceptible to trimethoprim-sulfamethoxazole (Table 4). 40.9% (9/22) of the patients had been treated with antibiotics for other infections within the previous year; in each case, cephalosporins consisting of cefazolin, cefuroxime and cefpirome were prescribed. However, the antibiogram and length of stay were not statistically different between those who were previously exposed to cephalosporins and those who were not (9.5 days vs. 13.7 days, $p = 0.357$) (Table 3).

Patients with *B. vesicularis* bacteremia received diverse antibiotic regimens. Most patients were treated with cephalosporins (12/22, 54.5%) but aminopenicillin with or without beta-lactamase inhibitor (ampicillin or amoxicillin-clavulanate), ureidopenicillin (piperacillin) or carbapenem (ertapenem) were also given. Of the 22 patients, 10 (45.5%) received inappropriate initial antibiotic therapy but there was no significant difference in length of hospital stay (11 days vs. 10 days). Most of the patients recovered from the infection and those who did not recover from infection received an intravenous antibiotic regimen (Table 3).

Discussion

B. vesicularis bacteremia is a clinical challenge for physicians due to a general lack of clinical experience within the medical community.[3–11,18] In this report, we described

Table 3 Summary of length of hospital stay, treatment regimen, treatment duration, antibiotic exposure within previous year, and outcome

Case	Previous antibiotic exposure	Antibiotic regimen	Hospital stay (d)	Treatment duration (d)	Outcome
1	N	Cefazolin	4	4	Survival
2	N	Cefazolin	14	8	Survival
3	N	Cefazolin	0	0	Survival
4	Cefuroxime	Clindamycin	6	5	Survival
5	N	Ceftazidime	24	10	Death
6	N	Gentamicin + Metronidazole	4	8	Survival
7	Cefazolin	Cefazolin/Cefpirome	10	5/5	Survival
8	Cefazolin	Cefazolin	0	0	Survival
9	Cefazolin	Ampicillin	40	23	Survival
10	N	Cefpirome	15	8	Survival
11	N	Piperacillin/Cefazolin	19	3/15	Survival
12	Cefazolin	Cephalexin	0	0	Survival
13	N	Ertapenem	10	8	Survival
14	N	Ceftazidime	7	7	Survival
15	N	Ceftazidime	7	6	Survival
16	N	Cefpirome + Metronidazole	6	4	Survival
17	Cefazolin	Ciprofloxacin	16	10	Survival
18	N	Cefazolin	5	4	Survival
19	Cefpirome	Amoxicllin-clavulanate/Cefpirome	33	8/11	Survival
20	N	Cephalexin	0	0	Survival
21	Cefazolin	Ciprofloxacin + clindamycin	8	8	Survival
22	Cefazolin	Amoxicllin-clavulanate/Ceftazidime + minocycline	10	8/8	Survival

N = no previous antibiotic exposure history; Nil = no antibiotic treatment.

22 cases of *B. vesicularis* bacteremia with 86.4% of cases being community-acquired. One-third of our patients were well prior to admission, in accordance with previous reports suggesting that *B. vesicularis* is able to cause invasive infections in healthy persons. However, the majority of patients in this study had chronic diseases such as hypertension, stroke and malignancy.

This report indicates that two-thirds of patients presented with fever at admission. Compared to afebrile patients, febrile patients had fewer comorbidities, shorter lengths of hospital stay, and lower levels of creatinine, AST, and ALT. These differences suggest that fever may serve as an important clinical clue for earlier diagnosis, empiric antibiotic therapy, and may contribute to a positive outcome.

This case series also consisted largely of patients with primary bloodstream infection without other associated infectious foci. *B. vesicularis* was not isolated from urine, sputum or pus specimens which may be explained by a higher rate of blood invasion by *B. vesicularis* or a reduced ability of the pathogen to compete with other bacterial flora. Further research is needed to clarify this issue. Both the favorable outcome (i.e., only one mortality) and the lack of significant prolonged hospital stays, even for those patients without appropriate initial empirical antibiotic therapy, indicated the low virulence for *B. vesicularis*.

The antibiotic susceptibility tests of the *B. vesicularis* isolates revealed that more than 90% were susceptible to cefpirome, piperacillin/tazobactam, and carbapenems, followed by aminoglycosides and ciprofloxacin. By contrast,

Table 4 Antimicrobial susceptibility of *Brevundimonas vesicularis* isolates using the agar dilution method

Antimicrobial agent(s)	MICs (mg/L)			Number (%) of susceptible isolates
	Range of MIC	MIC_{50}	MIC_{90}	
Ceftazidime	0.125—>128	2	32	14 (63.6)
Cefpirome	0.03125—128	0.125	4	20 (90.9)
Piperacillin with tazobactam	0.25/4—256/4	4	16	20 (90.9)
Imipenem	0.125—64	0.125	2	20 (90.9)
Ciprofloxacin	<0.015625—64	0.25	4	19 (86.4)
Gentamicin	1—>64	1	16	19 (86.4)
Amikacin	2—>512	2	16	19 (86.4)
Trimethoprim with sulfamethoxazole	0.25/4.75—>32/608	0.5/9.5	>32/608	13 (59.1)

MIC_{50} = minimum concentration required to inhibit the growth of 50% of microorganisms; MIC_{90} = minimum concentration required to inhibit the growth of 90% of microorganisms.

only 60% of strains were susceptible to ceftazidime and trimethoprim-sulfamethoxazole (Table 4). A review of literature revealed antibiograms for *B. vesicularis* conducted only on a single or a few strains based on the Kerby-Bauer diffusion method without the application of updated CLSI guidelines.[3,4,7,8,11,17] Compared with a recently published article, *B. vesicularis* isolates are 100% sensitive to piperacillin/tazobactam and amikacin but only 27% and 3% sensitive to cefepime and ceftazidime, respectively, based on MICs obtained by the agar dilution method.[19] Therefore, piperacillin/tazobactam, imipenem, and cefpirome are suggested for the treatment of *B. vesicularis* infection.

Our study had several limitations. The study was retrospective and conducted in a single tertiary hospital serving a population of two million. There were an inadequate number of patients to draw broad conclusions from and no information obtained from long-term care facilities. However, to the best of our knowledge, *B. vesicularis* infection has been reported only rarely in the published literature. Therefore, we can conclude that *B. vesicularis* causes community-acquired and low-mortality bloodstream infections, and that the resistance of this microorganism to trimethoprim-sulfamethoxazole and ceftazidime limits the choice of antibiotics for its management.

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